Susan Eik Filstead Stroke & Epilepsy Foundation, Inc.

A cure is at the ♥ of our mission.

July 26, 2004

Nancy Myers
Docket #2004-N-0181
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Critical Path Project and Epilepsy

On behalf of the 2.3 Americans living with epilepsy, including myself, I am writing to encourage members of the Critical Path Project to consider selecting epilepsy as the disease which merits elevation in priority for clinical research.

Unlike thousands of others living with intractable epilepsy, I know how wonderful life can be without epilepsy. I lived 38 years without a seizure, without debilitating side effects of seizure medication and without any horrific brain surgeries.

At the age of 38, I had a catastrophic stroke the morning after the birth of my son. At that time, I couldn't imagine anything worse than not being able to hold my newborn son. I quickly discovered things could be worse when I had my first seizure. After my second seizure I was told I had epilepsy resulting from the significant damage caused by the stroke.

Thus began my ongoing battle with epilepsy. More than my stroke, epilepsy has robbed me of precious time with my son. Fortunately, my son is not aware of all the times I wasn't able to respond to his needs because of hospitalizations, doctor's visits and side effects from seizure medications. My son is now 11 years old and has become painfully aware of the risks I face everyday. Numerous times he has witnessed paramedics rush me to the ER. He has faced the responsibility of calling 911 to get help while I was having a seizure which wouldn't stop. His heroic action saved my life and was acknowledged by the Boy Scouts of America.

Elevating epilepsy to the top of the list for clinical research would offer much needed hope to the individuals and their families struggling with this debilitating disease.

Thank you in advance for your time and consideration.

Sincerely,

Susan Eik Filstead

Susan Eik Filstead

2004N-0181

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Re: Critical Path Proposal and Epilepsy

I am writing this letter in support of epilepsy being placed on the list of diseases/conditions for consideration by the Critical Path Program of the FDA.

You are probably well versed in the scope of this problem: 2.3 million Americans have epilepsy; 55 million worldwide; about 1/3 to 40% of those who have epilepsy do not have any effective way to manage it. In these cases, epilepsy is refractory. It has been suggested that stroke is the leading cause of epilepsy in individuals over 50 years of age.

Numbers pale in comparison to the personal devastation this illness can have on an individual and their family. Epilepsy discriminates against no one, but to know someone with epilepsy is to be privy to the horrendous suffering it causes.

My wife, Susan, has epilepsy. Epilepsy began at 38 years of age the result of a stroke the day after our son was born and the subsequent development of an infection in her brain. The bleed caused damage; surgery to save her life added to the damage (the scaring); the infection left its mark- all eventually leading to epilepsy surgery in hopes of reducing or eliminating the seizures. Surgery was unsuccessful.

Having tried all drugs available to treat epilepsy and having undergone unsuccessful epilepsy surgery – the latest suggestion for addressing the relentless seizing is a functional right hemispherectomy. In short, the proposal is to disconnect the right side of her brain.

The current array of medications are a mixed blessing in that while they may contain or minimize the seizing activity, they leave the person in a "brain fog" – unable to clearly think, concentrate or use cognitive/intellectual faculties to their capacity. Not taking the medication risks uncontrolled seizing (status) and potentially sudden death.

So the choices are: brain fog from medications; status from uncontrolled seizures; or disconnection/removal of parts of her brain. There certainly must be better options.

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SEEKING ANSWERS:

THE FIND A CURE FOR EPILEPSY CONFERENCE

WILLIAM J. FILSTEAD Ph.D

MAY 18-20, 2003

LAKE BLUFF, ILLINOIS

This conference made possible through generous grants from: The Susan Klingenstein Fund and the Susan Eik Filstead Stroke and Epilepsy Foundation, Inc.

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Comments and remarks contained in this report are those of the author and do not necessarily represent the views of these foundations.

GENERAL DISCUSSION: MOVING AHEAD

A wide-ranging discussion occurred at the end of the conference, which focused on: 1) things to do, 2) the next step(s), and 3) remarks in general. A flavor of these discussions follows:

A point was made that seizures appear to be common to most, if not all, epilepsies. Seizures can be characterized as two-dimensional: 1) there can be a focus and 2) there can be a spread. While the focus varies greatly, the spread, one cell to another – one neuron to another, is common to all types of seizures. What factor contributes, causes, and participates in, the propagation of a seizure?

Politically, it is imperative that the nature and level of federal funding for epilepsy be understood. How much is being spent on what projects by which agencies?

Many diseases and conditions cut across NIH Institutes. Funding and collaborative efforts should reflect this collection of individuals with the condition as well as the complexity of the various manifestations of epilepsy. For example, epilepsy has implications for the National Institute on Aging, the National Institute on Child Health and Human Development, and NINDS to name but three of the obvious Institutes.

The focus of funding needs to be the condition(s) and not the vested territorial interest of specific Institutes or Centers.

In the NIH appropriation request before the 106th Congress there was specific language from both the House and the Senate that directed NIH to establish an Interagency Epilepsy Coordinating Committee to coordinate efforts among Institutes other than NINDS. This language also stressed the importance of setting aside funds for epilepsy research from Institute budgets other than NINDS (emphasis in text done by author).

From Senate NIH OD language:

"Epilepsy **- The Committee recognizes that while the NINDS is the primary Institute for addressing epilepsy, several other Institutes are also involved in related research**. As 75 percent of epilepsy cases begin in childhood, the NICHD has an important role to play in studying this disease. So, too, does the NHGRI, which is urged to assist the NINDS in the search for a genetic fingerprint diagnostic test aimed at improving drug therapy for epilepsy, and the NIMH, which is urged to explore the link between epilepsy and mood disorders, both of which are often treated with anticonvulsant medications. Finally, the NIA is encouraged to examine epilepsy in patients over age 65. The Committee urges the Director to coordinate research efforts among all these Institutes through an Interagency Epilepsy Coordinating Committee that includes agency scientists and industry and patient representatives."

Furthermore, NINDS was specifically directed by language from both the House and Senate to establish a coordination mechanism for opening communications among the Institute vis a vis Epilepsy.

From Senate NINDS language:

"Epilepsy **- The Committee believes that NIH should make finding a cure and effective treatments for epilepsy a priority. The Committee is encouraged by the**

establishment of 13 epilepsy research benchmarks resulting from the NINDS March 2000 conference "Curing Epilepsy: Focus on the Future." The Committee encourages NIH to develop a plan to implement the research benchmarks, as the Director deems appropriate, including the funding projections needed to carry out the plan. The Committee directs that the plan be submitted to Congress by April 1, 2002. Further, the Committee encourages the establishment of an Interagency Epilepsy Coordinating Committee comprised of agency scientists, industry, and patient representatives."

From House NINDS language:
"Epilepsy **-- The Committee is encouraged by the development of 13 benchmarks for epilepsy research resulting from the Institute sponsored conference held in March 2000 on "Curing Epilepsy: Focus on the Future"... The Committee urges NINDS to enhance research efforts in the prevention, treatment and eventual cure of this disease through all available mechanisms, as appropriate, including the development of a plan to implement the research benchmarks** and establishment of an Interagency Epilepsy Coordinating Committee. The Committee also urges the Institute to enhance efforts to address research issues related to the impact of seizures on young children, women, the elderly and those with intractable or uncontrolled epilepsy. NINDS is also encouraged to develop research plans and goals for the anti-epileptic drug development program. The Director should be prepared to testify on its efforts to advance these areas of research at the fiscal year 2003 appropriations hearing."

This renewed focus on epilepsy was included within Institute directives:

From Senate NHGRI language:
"Epilepsy - The Committee encourages the Institute to intensify its efforts to identify epilepsy genes for the more than 40 different types of epilepsy, **and to assist the NINDS in the search for a genetic fingerprint diagnostic test aimed at improving drug therapy for epilepsy. The Committee suggests that the Institute coordinate efforts with the NINDS to create a national consortium to identify new epilepsy susceptibility genes through a large-scale genotype:phenotype screen.** The Committee urges the Institute to make research in epilepsy a priority and to coordinate research efforts with other Institutes through the Interagency Epilepsy Coordinating Committee comprised of agency scientists and industry and patient representatives."

Clearly, expanding the research funds available for epilepsy by including other relevant Institutes (besides NINDS) is an excellent idea, but the funding of such an undertaking needs to be monitored. Each of the aforementioned Instituted (NIMH, NIA, NHGRI, etc) should set aside a percentage of their budget in line with the scope and impact of epilepsy.

Such an allocation of resources beyond those of NINDS would significantly increase the "pot of money" available to focus on epilepsy.

To date, neither the proposed committees nor any earmarked epilepsy funds outside of NINDS has occurred. Furthermore, why is it difficult to obtain an actual dollar amount that relates to specific problems? For popular issues such as AIDS the dollar figure is readily known – what about other less public illnesses such as epilepsy.

It is vitally important to know what funds are being spent on what specific research activities in order to have a clear sense of the resources behind what specific research tracks.

At the university level issues of overhead and tenure act as barriers to large-scale cooperative consortiums. Basic science needs to be seen in the same light as multi-center clinical trials. Basic science, which is the underpinning of much that was discussed, should have access to these multi-site collaborative research center grants.

The public does not seem to know epilepsy . There is a no "face" that can be attached to this disease like Michael J. Fox can be linked to Parkinson Disease or Christopher Reeve to spinal cord injuries. Epilepsy still is stigmatized which results in misconceptions and misunderstandings as to what it is.

Various efforts to create a gene data bank or a tissue bank focused on epilepsy would enhance research efforts. Blood samples of patients with and without epilepsy could be stored in this data bank of analysis. If susceptibility genes could be identified, then mouse models could be used to test compounds.

How many individuals have epilepsy? What types with what consequences? Perhaps an extensive epidemiological project could begin which aims to provide up to date data on the incident and prevalence of this problem. What is the ratio of children to adults? What proportion of cases have a known vs. unknown etiology? What is the relative effectiveness of which medication(s) for whom? How is the quality of life affected? What can be done to promote and enhance research funding for epilepsy? These are basic fundamental questions that need current information.

No seizures. No side effects. These are the current objectives of many who study, treat, and live with epilepsy. Short term it is vital to understand how seizures occur (predicting seizures onset is a goal) and why a seizure stops.

A longer view focus upon mouse models for testing compounds and understanding the role genes play in epilepsy.

Ultimately the goal is a cure – for those living with epilepsy and intervention strategies to prevent epilepsy from occurring.

This day will come and we trust this conference can speed this process along.

Table 1.
Conference Attendees

PARTICIPANTS	AFFILIATIONS
Nihal C. deLanerolle D.Phil D.Sc	Yale University School of Medicine
Marc Dichter MD Ph.D	University of Pennsylvania Medical School
Raymond Dingledine Ph.D	Emory University School of Medicine
Jerome Engel Jr. MD Ph.D	Reed Neurological Research Center UCLA School of Medicine
Gregory Holmes MD	Dartmouth Medical School
Leon D. Iasemidis Ph.D	Arizona State University
James O. MacNamara MD	Duke University School of Medicine
David McKinnon Ph.D	SUNY Stony Brook
Istvan Mody Ph.D	UCLA School of Medicine
Louis J. Ptacek MD	University of Utah School of Medicine
Michael A. Rogawski MD Ph.D	Epilepsy Research Section/NINDS
Paula Schauwecker Ph.D	Keck School of Medicine at USC
CONFERENCE FACILITATORS	
Jorge J. Asconapé MD	
William J. Filstead Ph.D	
CONFERENCE RECORDERS	
Amy Filstead MS	
Riley Snook MD	
GUESTS	
Susan Axelrod	
Susan Eik Filstead	
Susan Klingenstein	

Table 2.
Specific Responses to the Focal Question

1.	Surrogate markers of epileptogenesis need to be developed. i. What factors put people at risk for epilepsy?
2.	A better understanding of the natural mechanisms that prevent epileptic changes/epileptiform activity needs to be developed. o An example is *epilepsia partialis continua:* intractable focal epilepsy, which doesn't spread - why doesn't it spread?
3.	What methods can be developed to aid in predicting epilepsy onset? o An example is using EEG or other methods to predict who will develop epilepsy and possibly initiate treatment before seizures begin.
4.	Bring geneticists and physiologists together to address issues central to epilepsy. o Also try to engage pharmaceutical companies to fund and facilitate drug development
5.	Look for new ways to design drugs and methods to deliver drugs to the brain. o Design drugs specifically for the epileptic brain (not normal brain).
6.	Need to understand the critical elements in brain changes after damage, which lead to epilepsy.
7.	Understand and explore novel targets for epilepsy (i.e. ion channels).
8.	Understand the changes that take place between preictal, interictal, and postictal states. o What are the changes in the state of the brain that occur to produce seizures?
9.	Discover new epilepsy genes. o By discovering epilepsy genes and their products, new treatment approaches can be developed.
10.	Update our understanding of the pathologic changes in epilepsy by applying new techniques (i.e. molecular profiling) in hopes of identifying new targets for therapy.
11.	Improve collaboration between basic science research and clinical trials by the formation of consortiums.
12.	Discover commonalities that underlie genetic pathways such as common transcriptional events that take place during the development of epilepsy.
13.	Validate an animal model of epileptogenesis o Construct mouse models of epilepsy which can be validated and stored in a central location so they can share between researchers.
14.	Attempt to understand the primary dysfunction underlying epilepsy. o Is epilepsy a circuit problem (a change in connections in the brain)? o Is epilepsy a synaptic problem (a change in strength of connections in the brain)? o Is epilepsy an intrinsic neuronal problem (a structural problem with the neurons)?
15.	Define a molecular basis for epilepsy.
16.	Understand the mechanism for spontaneous remission in epilepsy.

	○ Develop experimental models (i.e. mouse models) to understand why epilepsy spontaneously remits in some patients.
17.	Understand what changes take place in the brain when an epileptic seizure stops. ○ Develop a mouse model to understand the mechanism(s) that "turn off' a seizure.
18.	Understand the differences in mouse genetics that produce different phenotypes in the animals despite being bred from the same genetic strain. ○ Why do pure-strain inbred mice express differences in respect of seizure parameters (threshold, remissions, etc.)? ○ Extrapolate differences in mice genotype/phenotype expression to human research.
19.	Develop better methods for identifying localizing seizure foci in epileptic patients. ○ Improvements in non-invasive and invasive localization methods could lead to more accurate (less morbid) surgical treatments.
20.	Understand the limitations of using animal models of epilepsy to predict human epilepsy. ○ Discover what parameters of animal epilepsy models can be applied to human epilepsies, and conversely, what factors are not applicable.
21.	Improve resolution of imaging and recording techniques in epilepsy.
22.	Understand the "direction of information flow" in epilepsy. ○ Solidify our understanding of the sequence and processes involved in seizures down to the molecular level.
23.	Develop a 3-dimensional "whole brain" understanding of brain structure and function vis a vis a seizure. ○ Explore the concept of "networks" of signaling and structural interaction.
24.	Develop animal models of drug-resistant epilepsy.
25.	Develop a better classification system for epileptic seizures and syndromes.
26.	Understand how a seizure may impact the development of future seizures. ○ Discover the mechanism by which "seizures beget seizures".
27.	Develop genetic animal models that can be used to produce pharmacogenetic profiles. ○ If several animal models can be developed and validated, they can be tested against current and investigational compounds. ○ This method could be used to develop an understanding of the best treatment for different types of epilepsy and lead to the discovery of new drug treatments.
28.	Form a consortium of non-epilepsy researchers to collaborate on the problem of curing epilepsy. ○ Bring together basic-science researchers who deal with ion channels, other physiologic processes to focus on processes involved in epilepsy.
29.	Develop techniques (stem cells, neuronal transplantation, etc.) to replace damaged neurons with healthy neurons.

30.	Work with politicians and lobbyists to decrease the bureaucracy and streamline the access for funding of epilepsy research.
31.	Focus on understanding some of the unique epilepsies of childhood (i.e. Lennox-Gastaut, infantile spasms) and extrapolate this knowledge to adult epilepsies.
32	Apply the emerging field of proteinomics to epilepsy research.
33.	Expand pathologic understanding by application of new techniques (molecular profiling). o Compare common pathologic substrates between different epilepsies to improve the general understanding of epilepsy.
34.	Explore reallocation of financial resources in drug research for epilepsy and search for ways to decrease pharmicoeconomic barriers to expanding the pool of drugs available to treat epilepsy. o Improve support for orphan drugs.
35.	Pool resources to try to cure a specific, known type of epilepsy (i.e. Juvenile Myoclonic Epilepsy). o After curing an epilepsy like JME the knowledge gained can be used to focus resources on other types of epilepsy.
36.	Understand how seizures propagate (what changes take place in the brain just before and just after a seizure starts). o Use this knowledge to try to prevent seizures before they start.
37.	Focus on improving epilepsy surgery in regards to localization, timing, etc.
38.	Understand the concept of hyper synchrony in seizure propagation.

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